REMARKS

Reconsideration is respectfully requested.

On entry of this amendment, claims 27-28, 34-38 and 48 have been amended. Claims 1-26, 29-33, and 39-47 are canceled. New claims 49-64 have been added. Claims 27-28, 35-38, and 48-64 are pending and under examination.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Support for the amendments to claim 27 may be found throughout the application. By way of example, support for "80% identical" may be found on page 21, lines 23-28; support for "mammalian" may be found on page 7, line 19; and support for "sequence specific degradation of a RNA transcript of the target gene by an endogenous system of the mammalian cell" may be found on page 17, lines 9-14. Thus the amendments do not constitute new matter.

Request for an Interview

Applicants request that the Examiner contact the undersigned in order to set up an interview to discuss the pending rejections and the following response to those rejections.

Rejections under 35 USC § 112, first paragraph

I. Rejection of Claims 34, 35, 40 and 48 under 35 U.S.C. § 112

The Examiner rejects claims 34, 35, 40 and 48 under 35 U.S.C. 112, first paragraph, as not properly enabled because the Examiner has asserted that the specification is not enabling of xenotransplantation.

The applicants respectfully disagree with the Examiner's rejection and assertion. The claims are not directed to a method of xenotransplantation and have utility outside of completely functional xenotransplants. One of the most obvious utilities of the claimed methods and

compositions is as research tools. The claimed invention demonstrates that utility by being capable of repressing the expression of the α-1,3-galactosyltransferase gene and thereby allowing researchers to explore the effect of repression of the α-1,3-galactosyltransferase gene on HAR and how much repression may be necessary to eliminate HAR. If the claimed invention completely eliminates or even lowers to a significant degree expression of the α-1,3-galactosyltransferase gene, this would allow researchers to begin addressing the other problems noted by McKenzie et al. Clearly, this demonstrates the utility of the claimed methods and compositions as research tools. The specification clearly enables one of skill in the art to make and use the claimed invention commensurate with this utility.

Since the specification of the present application is fully enabling for the claimed function and such function readily meets the standard for utility, applicants respectfully request that this ground for rejection be withdrawn.

II. Rejection of claims 1-13, 17, 18, 43 and 47 under 35 U.S.C. § 112

The Examiner rejects claims 1-13, 17, 18, 43 and 47 under 35 U.S.C. 112, first paragraph. Applicants respectfully disagree with the Examiner's grounds for rejection. However, in order to facilitate prosecution in this case applicants have canceled claims 1-13, 17, 18, 43, and 47, without prejudice or disclaimer. Applicants respectfully request that this ground for rejection be withdrawn.

Double Patenting

Claims 27, 38, 43, and 47 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,573,099.

Applicants respectfully disagree with the Examiner. The pending claims as currently amended are not obvious in light of the issued U.S. Patent No. 6,573,099. Claims 43 and 47 have been canceled. The independent claims 27 and 38 currently include the limitation "mammalian" while claims 1 and 6 in U.S. Patent No. 6,573,099 are limited to "animals," which

is a broad genus that encompasses mammals as well as other classes such as reptile, amphibians, fish, birds and several other classes in the Phylum Chordata as well as broader categories of animals falling into other phyla including Arthropoda, Mollusca, Annelida, Echinodermata and many more phyla in the animal kingdom. Nothing in claims 1 or 6 in U.S. Patent No. 6,573,099 would suggest selection of mammals versus any other classes or even phyla of animals. Thus, since the currently pending claims 27 and 38 are not obvious in light of claims 1 and 6 in U.S. Patent No. 6,573,099, applicants respectfully request that the Examiner withdraw the obviousness-type double patenting rejection.

Rejection under 35 USC § 102

A. Rejection under 35 USC § 102 of Claims 27, 28, 36 and 37

The Examiner rejects claims 27, 28, 36 and 37 under 35 U.S.C. 102(b) as being anticipated by Dorer *et al.* (1994) 77:993-1002 (made of record in the IDS filed 14 May 2001).

Claim 27 recites "An isolated deoxyribonucleotide molecule comprising at least two copies of a target gene or region thereof which are at least 80% identical to the sequence of the target gene or region thereof,

wherein a first copy is in the sense orientation, and a second copy is in the antisense orientation; and

wherein the isolated deoxyribonucleotides molecule is capable of ***post-transcriptionally*** repressing, delaying, or otherwise reducing expression of said ***target gene*** when expressed in a ***mammalian*** cell by sequence-specific degradation of a RNA transcript of the target gene by an endogenous system of the ***mammalian*** cell." (Emphasis added.) Claims 28, 36, and 37 depend from claim 27.

Dorer et al. fail to teach all limitations of the amended claims.

As discussed in the response submitted on September 8, 2003, Dorer et al. fail to teach ***post-transcriptional*** repression.

In addition, as discussed in the response submitted on September 8, 2003, Dorer et al. fail to teach repression of a ***target gene***. The construct of Dorer et al. represses its own expression. There is no evidence that it represses any other gene that could be considered a target gene.

Further, claim 27 as amended is limited to repressing, delaying or otherwise reducing target gene expression in a ***mammalian*** cell. Dorer et al. teach a construct for use in a Drosphila system. Drosphila is not a mammal. Since Dorer et al. fail to meet every limitation of claim 27, Dorer et al. also fail to meet every limitation of claims 28, 36 and 37, which depend from claim 27. Specifically, Dorer et al. fail to teach a construct that is capable of repressing, delaying or otherwise ***post-transcriptionally*** reducing expression of a ***target gene*** in a ***mammalian cell***. In order to anticipate a claimed invention, a reference must teach every limitation of the claimed invention.

Applicants respectfully request that the rejection of claims 27, 28, 36 and 37 under 35 U.S.C. 102(b) be withdrawn.

B. Rejection under 35 USC § 102 of Claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47

The Examiner rejects claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,506,559 to Fire *et al* (U.S. Patent '559).

The Examiner has asserted that Fire *et al.* teach introduction of DNA into an animal cell as claimed in the present invention. The applicants respectfully disagree that the vague statements in Fire *et al.* teach such introduction of DNA into an animal cell at all, much less in a manner that would enable one of ordinary skill in the art to make and use DNA constructs as claimed in the present application. The Examiner has asserted that the U.S. Provisional Application (60/068,562) that is the priority application of Fire *et al.* supports the introduction of DNA into an animal cell to repress a target gene. However, it is very clear from the context of the sections that the Examiner is citing to that the discussions of RNA synthesis *in vivo* are referring to a method of synthesizing the RNA for later introduction of the RNA. First, with regard to the first paragraph on page 7 cited by the Examiner, the text of the two relevant sentences of the paragraph has been repeated below.

> "RNA may be synthesized either *in vivo* or *in vitro*. Endogenous RNA polymerase of the cell may mediate transcription *in vivo*, or cloned RNA polymerase can be used for transcription *in vivo* or in *vitro*."

The language of this paragraph speaks to synthesis of the RNA, not introduction of the RNA. The paragraph on page 11 starting at line 17 further supports this interpretation. For convenience, the first two sentences of the paragraph are reproduced below.

> "RNA may be chemically synthesized by manual or automated reactions. The RNA may be synthesized by RNA polymerase of the cell or a bacteriophage RNA polymerase (e.g., T3, T7, SP6)."

Here again, the reference clearly is speaking about methods of ***synthesis*** of the RNA to be introduced into the cell. The language in each paragraph clearly refers to ***synthesis*** of the RNA, not ***introduction*** of the RNA into a cell. The second sentence discusses viral polymerases. It is worth pointing out that the only viral polymerases mentioned are bacteriophage polymerases. Bacteriophages are viruses which attack prokaryotes, not eukaryotes. This again suggests that this is referring to a method of synthesizing the RNA in a prokaryote to later be introduced into the appropriate organism.

The last section cited by the Examiner is on page 12 lines 10-12. "A viral vector packaged into a viral particle would accomplish both efficient introduction of an expression vector into the cell and transcription of RNA encoded by the expression vector." This sentence is at best ambiguous. It could refer to introduction of an expression vector into an animal cell as asserted by the Examiner. However, it could also be discussing a method of synthesis of the RNA for later introduction into the animal cell. This latter interpretation is more consistent with the rest of the application where the examples and the discussion all relate to introduction of RNA into *C. elegans*. Further, the cited sentence on page 11 clearly contemplates use of bacteriophage RNA polymerases without mentioning a single eukaryotic viral polymerase which would be consistent with this sentence on page 12 referring to use of a bacteriophage viral vector to produce RNA in prokaryotes for later introduction into an animal cell.

Finally, while it is a provisional application, the applicants chose to include claims. Those claims support the fact that the applicants were referring to a method of synthesis. Claim 1 as the independent claim sets out the basic method of "introduction of a ribonucleic acid

(RNA) into the cell..." The dependent claims 6-9 set out various cell types referring to "the cell," which has antecedent support as a cell in the first line of claim 1. Dependent claims 18-19 add two methods by which "the RNA is introduced ..." Claim 20, the last claim, is significant in that it refers to the method of producing the RNA as "an expression vector in ***a cell*** produces the RNA." The claim refers to "a cell", not "the cell". Because this claim uses the indefinite article "a," it is not referring back to the same cell mentioned in the independent claim 1, rather it is a different cell than the cell referred to in the independent claim 1. Thus claim 20, the only claim that refers to production of RNA within a cell clearly refers to synthesis in one cell and then introduction into another a different cell. Thus, the most reasonable interpretation of the provisional application is that it does not include introduction of a DNA based expression vector into an animal cell. It instead refers to a method of synthesizing RNA in a prokaryote for later introduction into an animal cell. Therefore, the priority date of the Fire patent as 102(e) art is the filing of the non-provisional application on December 18, 1998, well past the priority date of the present application.

Furthermore, the applicants have amended the pending claims, without prejudice or disclaimer, to recite introduction of DNA into ***mammalian*** cells and such DNA constructs. Fire et al. fail to anticipate the amended claims. The Examiner's reasons for rejection are thus also obviated by the amendments.

U.S. Patent '559 to Fire et al. does not anticipate repressing, delaying, or otherwise reducing the expression of a target gene in a ***mammalian*** cell by introducing DNA to a ***mammalian*** cell as required by the amended claims. As discussed in the previous response, the provisional application that the '559 Patent claims priority to only discloses methods of gene silencing by introducing dsRNA directly into nematodes; an animal that is not mammalian and not even vertebrate. Fire et al. do not present a single example either prophetic or otherwise for creating and/or introducing a DNA construct expressing dsRNA into any animal much less a mammal in the provisional application. The Examiner has noted that not even Andrew Fire, one of the inventors of Fire et al., believed that dsRNA would work in mammals. As cited by the Examiner in the Office Action mailed March 7, 2003, Fire in Fire (1999) *Trends Genet. 15:358-363)* teaches "[f]rom a technical perspective, one could certainly hope that RNA-triggered silencing would exist in vertebrates: this would facilitate functional genomics and might allow

medical applications involving targeted silencing of 'renegade' genes. Although this hope is not ruled out by any current data, the simple protocols used for invertebrates and plant systems are unlikely to be effective. Mammals have a vehement response to dsRNA ..." Clearly, without an example that would work in a mammal, one of skill in the art would not know how to apply the teachings in the provisional application, which is the alleged priority application of Fire *et al.*, to a mammal. By contrast, the present application sets forth actual examples that, as discussed above, are in fact functional in mammals.

Fire et al. thus clearly fail to contemplate introducing DNA to a ***mammalian*** cell in which expression of a target gene is repressed, delayed, or otherwise reduced and fail to enable the same through the failure to provide a single example either prophetic or otherwise.

The Examiner's reasons for rejection are obviated by the amendment. Since the priority application to U.S. Patent '559 of Fire et al. fails to teach every limitation of the claims given that it does not teach mammalian cells. Furthermore, the priority application fails to disclose introduction of DNA to an animal cell of any kind to repress, delay, or otherwise reduce the expression of a target gene.

Therefore, U.S. Patent No. 6,506,559 does not qualify as § 102(e) prior art because the priority application fails to anticipate the claimed invention. Furthermore, claims 1, 2, 12, 17, 18, 43 and 47 have been canceled.

Applicants respectfully request that the rejection of claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47 under 35 U.S.C. 102(e) be withdrawn.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant(s) petition(s) for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. **546322000321**.

Respectfully submitted,

Dated: December 7, 2004 By: _____

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